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Submitting Organization
EASTMAN KODAK CO

Contractor

Document Title
INITIAL SUBMISSION: ACUTE AND SUBACUTE INHALATION TOXICITY OF 2,4-DIIOCYANATO-1-METHYLBENZENE IN GUINEA PIGS AND RATS, RESPECTIVELY, WITH COVER LETTER DATED 092892

Chemical Category
2,4-DIISOCYANATO-1-METHYLBENZENE

8(e)

CAP

(COMPLIANCE AUDIT PROGRAM)

10955

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September 28, 1992

Document Processing Center (TS-790)
Office of Pollution Prevention and Toxics
U. S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
Attn: 8(e) Coordinator (CAP Agreement)

Dear Sir or Madam:

Subject: Report submitted in accordance with guidelines established by the U. S. Environmental Protection Agency Registration and Agreement for the TSCA 8(e) Compliance Audit Program

Report submitted by: Eastman Kodak Company
343 State Street
Rochester, NY 14650
(716) 724-4000
CAP Agreement Identification Number (8ECAP-0039)

This report pertains to 2,4-diisocyanato-1-methylbenzene (synonyms: tolylene-2,4-diisocyanate; TDI; compound 75-04) [CAS # 584-84-9] and is being submitted because of effects observed in a subacute inhalation study in rats. This report is being identified as a study involving other than human effects (Unit II.B.2.b of CAP Agreement).

A group of five male rats was exposed to an inhalation concentration of 26 ppm for six hours per day, five days per week for one week. This was followed by a three week rest period and a second one week exposure period. One animal died during the last exposure of the second exposure period, while another died 48 hours after the last exposure. The survivors were euthanatized three days after the final exposure. Histopathologic findings included degenerative changes of the tracheal and bronchiolar epithelium and alveolar hemorrhage, edema, and inflammatory cell accumulation.

In a second experiment, two groups of five female guinea pigs were exposed to 26 ppm of the test compound for 6 hours per day. One group was previously exposed to the test compound by footpad injection. The animals were euthanatized on the day following exposure. There were no histopathologic differences between the two groups in terms of type, relative occurrence, and distribution of cells.

Questions regarding this submission should be addressed to:

Mr. William Hart
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Sincerely,

for

R. Hays Bell, Ph.D.
Vice President
Corporate Health, Safety and Environment
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RHB:JAF
Enclosures

INHALATION Chemical: Tolylene-2,4-diisocyanate

KP# 54295

Chemical Formula Type of Exposure	Animals* No. and Species	Conc.	Time	Mortality	Symptoms
3.0 L/min airflow through a gas washing bottle at room temperature. Chamber temperature, 21 - 23 C.	5 R	0.185 mg/l (26 ppm)	1st 5 days expo. 6 hr/day	0/5	Blinking - 1 min. Nose rubbing - 1 min. Dyspnea - slight after 2nd expo. and thereafter 7 day wts. - 4-(44 g.av.) 1+(18 g)
			21 days no exposure	0/5	No symptoms 21 day wts. - 5+(91 g.av.)
			2nd 5 days expo. 6 hr./day	1/5 5th expo. 2/5 48 hr post expo.	Blinking - 1 min. Nose rubbing - 1 min. Dyspnea - 3 hr into 2nd expo. and thereafter, sl. to mod. Deaths - 1 rat died after 6 hr. into the 5th exposure 1 rat died 48 hrs after the 5th exposure 7 day wts. - 3-(80 g.av.) 35 day wts. - 3+(29 g.av.)
(Control rats #21-25)					

* G.P. - Guinea Pig, M - Mouse,
R - Rat, RB - Rabbit

INHALATION Chemical: Tolylene-2,4-diisocyanate

KP# 54295

Chemical / Type of Exposure / Formula	Animals* No. and Species	Conc.	Time	Mortality	Symptoms
Controls for 75-04, 74-362, 74-364, 74-365					
3.0 L/min airflow. Chamber temperature, 21 - 22 C.	5 R	0	1st 5 days expo. 6 hr/day	0/5	No symptoms 7 day wts. 5+(35 g.av.)
			21 days no exposure	0/5	No symptoms 21 day wts. 5+(93 g.av.)
			2nd 5 days expo. 6 hr/day	0/5	No symptoms 7 day wts. 5+(146 g.av.)

* G.P. - Guinea Pig, M - Mouse,
R - Rat, RB - Rabbit

75-04
Tolylene-2,4-diisocyanate

Five male rats were exposed to 26 ppm of compound 75-04 in 18 liter inhalation chambers for six hours per day, five days per week followed by a three week rest period and a second similar exposure. Two animals died prematurely; the remainder were killed on the third post-exposure day with an overdose of sodium pentobarbital IP.

Trachea, lung, liver, kidney, heart, adrenal gland, spleen, bone marrow and mesenteric lymph node were fixed in 10% neutral formalin and examined by light microscopy. The lungswere perfused with formalin via the trachea.

Tracheal epithelium has undergone degenerative changes over a large area. Excessive exfoliation and sloughing contribute to the debris present in the lumen. Hyperemia, edema, and inflammatory infiltrates are common in tracheal submucosa. The changes are most severe in the animals dying prematurely producing occlusion of the lumen by purulent debris and edema and hemorrhage in connective tissue adjacent to the trachea.

Bronchial epithelium is flattened and degenerating in many areas with hyperplasia and excessive exfoliation noted elsewhere. Polymorphonuclear leukocytes lightly infiltrate these areas. A minor number of small bronchi are occluded with purulent debris and heavily infiltrated by leukocytes. In the two more severely affected animals, a majority of the bronchi, large and small, are occluded.

Alveolar abnormalities are more variable in occurrence. In two animals, a minor but significant portion of the field is affected while in the others a major portion is involved. Patchy areas of hemorrhage, edema, alveolar and interstitial inflammatory cell accumulation and atelectasis are less extensive than with compound 74-364. Perivascular edema and lymphoid accumulation varied between animals. Peribronchial lymphoid follicle depletion, more widespread involvement of alveoli and rupture of alveolar walls were associated with early death. Eosinophile collections in the interstitial space and more especially around blood vessels and bronchi were frequently heavy in three out of five animals.

The thymus in one instance had areas of hemorrhage and erythrophagocytosis. Focal necrosis of small numbers of hepatic cells and periportal hepatic necrosis occurred only in dying animals. Both livers were also congested. Renal tubular epithelium and collecting duct epithelium contained segments with pynotic, fragmented nuclei in dying animals. These animals also had hypocellular, edematous bone marrow, depletion of splenic lymphoid follicles and agonal myocardial edema and hemorrhage.

John L. O'Donoghue, VMD
Toxicology Section
Health and Safety Laboratory

JLO:bdo
5-21-75

74-362, 74-364, 74-365 and 75-04
Control

Five male rats used as controls for compounds 74-362, 74-364, 74-365 and 75-04 were exposed to compressed air for six hours per day, five days per week with a three week rest period and a second similar exposure. All animals were killed with an overdose of sodium pentobarbital IP.on the third day after the last exposure.

Trachea, lung, kidney, heart, adrenal gland, spleen, bone marrow and mesenteric lymph node were fixed in 10% neutral formalin and examined by light microscopy. The lungs were perfused with formalin via the trachea.

Slight to moderate perivascular, peribronchial and interstitial accumulations of lymphocytes were present. In one animal, there was a diffuse alveolar macrophage proliferation associated with intracellular accumulations of a golden granular pigment. Two small areas of hemorrhage were also seen.

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JLO:bdo
5-21-75

TOXICITY REPORT - E. K. CO. - LABORATORY OF INDUSTRIAL MEDICINE

INHALATION Chemical: Tolylene-2,4-diisocyanate

KP# 54795

Chemical Formula Type of Exposure	Animals* No. and Species	Conc.	Time	Mortality	Symptoms
3.0 L/min airflow through a gas washing bottle at room temperature. Chamber temperature, 23 C.	6 G.P.*	0.185 mg/l (26 ppm)	6 hr.	0/6	Blinking - 1 min. Nose rubbing - 1 min. Sacrificed 20 hr. post exposure
3.0 L/min airflow through a gas washing bottle at room temperature. Chamber temperature, 23 C.	4 G.P.	0.185 mg/l (26 ppm)	6 hr.	0/4	Blinking - 1 min. Nose rubbing - 1 min. Sacrificed 20 hr. post exposure

*Half of each exposure group was sensitized by the following methods:

Footpad injection-1% in rabbit blood 10 days before exposure; drop on-0.01% in solvent control 3 days before exposure; remainder of the guinea pigs served as controls.

* G.P. - Guinea Pig, M - Mouse,
R - Rat, RB - Rabbit

75-04

Tolylene-2,4-diisocyanate

Two groups of five female guinea pigs were exposed to 0.185 mg/l of compound 75-04 for six hours in 18 liter inhalation chambers. One group had previously been exposed to the test compound by footpad injection. The following day the animals were killed with an overdose of sodium pentobarbital IP. The trachea, the thyroid gland, lung and regional lymph nodes were perfused with 10% neutral formalin through the trachea and placed in the same fixative. No difference between the two groups could be detected on histopathologic examination. Inflammatory infiltrates consisted of the same cell types, the same relative occurrence of cell types and the same distribution of cell types. The severity of changes was indistinguishable between the groups.

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5-13-75

A Comparison of Compounds 74-362, 74-364, 74-365 and 75-04 after Exposure to Guinea Pigs by Inhalation

In this series of experiments, an attempt was made to sensitize female guinea pigs to each compound by footpad injection and then expose them and a control group of naive guinea pigs to the same compound by inhalation, trying to produce an acute allergic response. With only one of the compounds (74-365) is there a possibility of an allergic response in that three out of five pre-treated animals had more extensive involvement of alveoli and a heavier cell infiltrate but even in this case the difference is not as dramatic as would be expected with an allergic reaction. The conclusion is that no acute allergic respiratory response was demonstrated with any of the compounds.

The histopathologic changes produced were used to rank the compounds as to the severity of changes occurring after a single massive insult. The compounds were not all delivered at the same concentration and did not produce injury in the same portion of the respiratory system. The comparison is based on the severity of the lesions produced and the probable acute distress produced in the animal.

Ranking in order of increasing severity of acute response:

1 - compound 74-365 0.093 mg/l - Hylene W
2 - compound 74-362 0.093 mg/l - CHMBI
3 - compound 75-04 0.185 mg/l - TDI
4 - compound 74-364 0.093 mg/l - Isophorone Diisocyanate

The pathologic changes due to compounds 74-365 and 74-362 were primarily due to alveolar changes (edema, hemorrhage, inflammatory infiltrates) with bronchial changes of secondary importance while with compounds 75-04 and 74-364 the changes were primarily bronchial producing airway obstruction and alveolar effects of secondary importance.

Compound 74-362 at 0.185 mg/l produced more widespread effects than at 0.093 mg/l as expected but still were not as serious as with compound 75-04. Compound 75-04 delivered at twice the concentration as compound 74-364 is ranked as less severe because 74-364 produced coagulation necrosis of bronchial epithelium in addition to other damage.

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JLO:bdo
5-14-75

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